(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 December 2002 (12.12.2002)

PCT

(10) International Publication Number
WO 02/098861 A1

(51) International Patent Classification[7]: C07D 231/56

(21) International Application Number: PCT/US02/16843

(22) International Filing Date: 30 May 2002 (30.05.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/295,427 1 June 2001 (01.06.2001) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/098861 A1

(54) Title: METHODS OF MAKING 1-(2-AMINOPROPYL)-6-HYDROXYINDAZOLE

(57) Abstract: Methods of making 1-(2-aminopropyl)-6-hydroxyindazole are described. The method involves, in part, reacting 4-benzyloxy-2-(2-hydroxypropyl)aminobenzaldehyde with an organic or inorganic nitrite to form 4-benzyloxy-2-(2-hydroxypropyl)nitosaminobenzaldehyde, wich in turn is reacted with a reducing agent with concomitant cyclization to form 6-benzyloxy-1-(2-hydroxypropyl)indazole. The 6-benzyloxy-1-(2-hydroxypropyl)indazole can then be transformed into 1-(2-azidopropyl)-6-benzyloxyindazole which in turn can be converted to the final product.

METHODS OF MAKING 1-(2-AMINOPROPYL)-6-HYDROXYINDAZOLE

This application claims the benefit under 35 U.S.C. §119(e) of prior U.S. Provisional Patent Application No. 60/295,427 filed June 1, 2001, and is incorporated in its entirety by reference herein.

BACKGROUND OF THE INVENTION

The present invention relates specifically to methods of making 1-(2-aminopropyl)-6-hydroxyindazole which avoid undesired side products.

WO 98/30548 (Yamanouchi) shows the utility of 1-(aminoalkyl)indazoles for treating CNS diseases. The route of synthesis involves the reaction of various indazoles, having substituents only in the benzene ring, with alkylating agents. It is well known that such alkylation of indazoles always gives about a 1:1 mixture of isomeric 1- and 2-alkylindazoles. See, generally, Song and Yee, Organic Letters, vol. 2, page 519 (2000). Therefore about half of the reaction material is wasted due to the formation of the undesired 2-alkylindazole which must be separated by chromatography or other technique. The isolated 1-alkylindazole is then further modified to provide the target 1-(aminoalkyl)indazole.

Fischer and Tafel, Justus Liebigs Annalen der Chemie, vol. 227, p. 334 (1885) report nitrosation of 2'-ethylaminoacetophenone with sodium nitrite and the reduction of the resulting nitrosamine with zinc to yield 1-ethyl-3-methylindazole. Use of isoamyl nitrite instead of sodium nitrite for an analogous nitrosation is discussed in Applegate and Turnbull, Synthesis, p. 1011 (1988). McGeachin, Canadian Journal of Chemistry, vol. 44, p. 2323 (1966) reports nitrosation of a 2-aminobenzaldehyde wherein the amino group is substituted with a nonhydroxylic $C_{23}H_{18}N_3O$ group, for the purpose of verification of chemical structure. The resulting nitrosamine was reduced with zinc forming a very specific indazole, for the purpose of further verification of chemical structure.

Monoalkylhydrazines react with benzophenones or acetophenones having *ortho* leaving groups (e.g., halide or mesylate) to give 1-alkylindazoles substituted at the 3-position as reported in Caron and Vazquez, Synthesis, p. 588 (1999). The analogous conversion of benzaldehydes to 3-unsubstituted indazoles requires forcing conditions unsuitable for scaleup. See Halley and Sava, Synthetic Communications, vol. 27, p. 1199 (1997).

Suwinski and Walczak, Polish Journal of Chemistry, vol. 59, p. 521 (1985), report cyclization of 2-aminobenzaldoxime hemisulfate to give indazole. The inventors attempted to extend this method to a 2-alkylaminobenzaldoxime hemisulfate, but the desired 1-alkylindazole was not obtained and instead the unwanted nitrile or the free oxime was obtained. An analogous cyclization of oxime acetates, demonstrated only for forming 3-substituted indazoles, employs conditions poorly suited for scaleup as shown in Brown et al., Journal of Medicinal Chemistry, vol. 35, p. 2419 (1992). Cyclization of 2-acylaminobenzaldoxime derivatives yields 1-acylindazoles (von Auwers and Frese, Justus Liebigs Annalen der Chemie, vol. 450, p. 290 (1926)) but these do not provide 1-alkylindazoles upon reduction, the 1-unsubstituted indazole being formed instead. See Al-Khamees and Grayshan, Journal of the Chemical Society, Perkin Trans. I, p. 2001 (1985). A known synthesis of 1,3-dialkylindazoles from 1,3-dialkylindoles involves (1) oxidative cleavage of the 1,3-dialkylindazole to give the 2-(N-alkylformamido)aryl alkyl ketone; (2) ketoxime formation with concurrent N-deformylation; (3) O-acetylation; and (4) heating the resulting ketoxime acetate at 170-200 °C in the melt, under vacuum. See Matassa et al., J. Med. Chem., vol. 33, page 1781 (1990); and Brown et al., J. Med. Chem., vol. 35, page 2419 (1992). This method has not been demonstrated for aldoximes, required for the synthesis of 3-unsubstituted indazoles. Furthermore, the in

vacuo thermolysis step has been reported on a maximal 1.3-gram scale, and would present experimental difficulties on a larger preparative scale.

Accordingly, there is a need to provide processes to manufacture 1-(2-aminopropyl)-6-hydroxyindazole which avoid undesired isomers and which are capable of producing scaleup quantities of the desired compound.

All patents, patent applications, and publications referenced in this application are incorporated in their entirety and form a part of the present application.

SUMMARY OF THE PRESENT INVENTION

A feature of the present invention is to provide a method to make 1-(2-aminopropyl)-6-hydroxyindazole.

A further feature of the present invention is to provide a method to make 1-(2-aminopropyl)-6-hydroxyindazole in large quantities and with avoiding large quantities of undesired isomers.

Additional features and advantages of the present invention will be set forth in part in the description that follows, and in part will be apparent from the description, or may be learned by practice of the present invention. The objectives and other advantages of the present invention will be realized and attained by means of the elements and combinations particularly pointed out in the description and appended claims.

To achieve these and other advantages, and in accordance with the purposes of the present invention, as embodied and broadly described herein, the present invention relates to a method of making 1-(2-aminopropyl)-6-hydroxyindazole involving

a) nitrosating 4-benzyloxy-2-(2-hydroxypropyl)aminobenzaldehyde to produce 4-benzyloxy-2-(2-hydroxypropyl)nitrosaminobenzaldehyde;

b) reacting said 4-benzyloxy-2-(2-hydroxypropyl)nitrosaminobenzaldehyde with a reducing agent to convert NO to NH_2 with concomitant cyclization to form 6-benzyloxy-1-(2-hydroxypropyl)indazole;

c) reacting said 6-benzyloxy-1-(2-hydroxypropyl)indazole with a sulfonyl halide or sulfonic anhydride to form the corresponding sulfonic ester which is reacted with a metal azide to yield 1-(2-azidopropyl)-6-benzyloxyindazole; and

d) reacting said 1-(2-azidopropyl)-6-benzyloxyindazole with a hydrogen source and a catalyst to yield 1-(2-aminopropyl)-6-hydroxyindazole.

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are intended to provide a further explanation of the present invention, as claimed.

DETAILED DESCRIPTION OF THE PRESENT INVENTION

The present invention relates to methods of making 1-(2-aminopropyl)-6-hydroxyindazole. The methods of the present invention preferably permit the making of 1-(2-aminopropyl)-6-hydroxyindazole on a large scale and preferably avoiding the formation of undesirable isomers. In more detail, Yamanouchi in WO 98/30548, in Reference Example 35, describes a preparation of compound **10**, wherein 6-benzyloxyindazole is reacted with propylene oxide and a base to give, after chromatographic purification, 6-benzyloxy-1-(2-hydroxypropyl)indazole (**8**). It is well known in the art that alkylation reactions of N-unsubstituted indazoles produce mixtures of isomeric 1-alkylated and 2-alkylated products, which must then be separated chromatographically or by other means. See, generally, Song and Yee, Organic Letters, vol. 2, page 519 (2000). The loss of material in the form of the undesired 2-alkylated product, for instance, is especially undesirable when enantiomerically enriched or enantiomerically pure final pharmaceutically active product (**10**) is desired.

For instance, a method for producing 6-benzyloxy-1-(2-hydroxypropyl)indazole (**8**) and its enantiomerically enriched or enantiomerically pure R or S forms, free of the isomeric 6-benzyloxy-2-(2-hydroxypropyl)indazole, is desired for use in the production

on a multigram or larger scale of 1-(2-aminopropyl)-6-hydroxyindazole (**10**) and its enantiomerically enriched or enantiomerically pure S or R forms.

In the methods of the present invention, the process can begin with 4-benzyloxy (2-hydroxypropyl)aminobenzaldehyde which is subjected to a nitrosation in order to form 4-benzyloxy-(2-hydroxypropyl)nitrosaminobenzaldehyde. Referring to the reactions being set forth in Scheme 1, various preferred compounds are referenced by their numerals in bold in Scheme 1. The 4-benzyloxy-(2-hydroxypropyl)nitrosaminobenzaldehyde (**7**), which is formed is then reacted with a reducing agent to convert NO to NH_2 with concomitant cyclization. The resulting compound, 6-benzyloxy-1-(2-hydroxypropyl)indazole (**8**) is formed to the exclusion of the isomeric 6-benzyloxy-2-(2-hydroxypropyl)indazole.

The described conversion of **6** to **7** to **8** can be effected using racemic compounds, or using entantiomerically enriched or enantiomerically pure compounds of either the R or the S absolute configuration.

The following sequences are provided to set forth preferred methods of making the compounds of the present invention. Furthermore, preliminary steps to the formation of the starting material, namely, the starting 4-benzyloxy-(2-hydroxypropyl)aminobenzaldehyde are also provided. For purposes of the present invention, the starting material can be formed by various methods and the methods set forth below are simply offered as examples of reaction schemes that can be used to produce the starting material for the methods of the present invention. Those skilled in the art will recognize, from a review of the present application, that other reaction schemes can be used to form the starting materials for use in the methods of the present invention.

Sequence A:

Step 1. 6-Benzyloxyindole (1) (Batcho and Leimgruber, Organic Syntheses, Collective Vol. 7, p. 34 (1990)) is reacted with (±)-propylene oxide and a base in an organic solvent to yield (±)-1-(2-hydroxypropyl)-6-benzyloxyindole (2). Preferably the base is sodium hydride and the solvent is tetrahydrofuran. The temperature is 0 °C to 25 °C, preferably about 10 °C. Preferably an inert atmosphere, e.g., nitrogen or argon, is maintained.

Alternatively, compound **1** is reacted with (*R*)-propylene oxide according to the foregoing method to yield (*R*)-1-(2-hydroxypropyl)-6-benzyloxyindole (*R*-2). Alternatively, compound **1** is reacted with (*S*)-propylene oxide according to the foregoing method to yield (*S*)-1-(2-hydroxypropyl)-6-benzyloxyindole (*S*-2).

Step 2. Compound **2** is reacted with ozone in an organic solvent, preferably dichloromethane, at –80 to –40 °C, preferably –55 to –70 °C, followed by addition of a reducing agent, preferably dimethyl sulfide. The temperature is then allowed to increase to about 25 °C, to yield (±)-4-benzyloxy-2-(N-(2-hydroxypropyl)formamido)benzaldehyde (3).

Alternatively, compound ***R*-2** is reacted according to the foregoing method to yield (*R*)-4-benzyloxy-2-(N-(2-hydroxypropyl)formamido)benzaldehyde (*R*-3). Alternatively, compound ***S*-2** is reacted according to the foregoing method to yield (*S*)-4-benzyloxy-2-(N-(2-hydroxypropyl)formamido)benzaldehyde (*S*-3).

Step 3. Compound **3** is reacted with a base or an acid in the presence of water and an organic solvent, to yield (±)-4-benzyloxy-2-(2-hydroxypropyl)aminobenzaldehyde (**6**). Preferably, base is used and the preferred base is sodium hydroxide or potassium hydroxide and the preferred solvent is tetrahydrofuran and the temperature is 0 to 35 °C, preferably 20 to 25 °C. Preferably, an inert atmosphere, e.g., nitrogen or argon, is maintained.

Alternatively, compound *R*-3 is reacted according to the foregoing method to yield (*R*)-4-benzyloxy-2-(2-hydroxypropyl)aminobenzaldehyde (*R*-6). Alternatively, compound *S*-3 is reacted according to the foregoing method to yield (*S*)-4-benzyloxy-2-(2-hydroxypropyl)aminobenzaldehyde (*S*-6).

Sequence B:

Step 1. 4-Benzyloxy-2-fluorobenzonitrile (4) is reacted with (±)-1-amino-2-propanol in an organic solvent, to yield (±)-4-benzyloxy-2-(2-hydroxypropyl)aminobenzonitrile (5). At least two molar equivalents of 1-amino-2-propanol are used, as one molar equivalent is consumed as the amine hydrofluoride. Alternatively an auxiliary base is employed, for example a tertiary amine such as triethylamine or N,N-disopropylethylamine, an alkali metal carbonate such as sodium carbonate or potassium carbonate, or basic alumina. When the auxiliary base is employed, less than two molar equivalents of (±)-1-amino-2-propanol can be used, preferably about 1.5 molar equivalents. Preferably an auxiliary base is employed, most preferably basic alumina. The solvent is preferably a dipolar aprotic solvent, for example dimethyl sulfoxide or N-methylpyrrolidone. The temperature is 80 to 140 °C, preferably 100 to 120 °C. Optionally, a drying agent; e.g., zeolite molecular sieves, is present.

Alternatively, compound 4 is reacted with (*R*)-1-amino-2-propanol according to the foregoing method to yield (*R*)-4-benzyloxy-2-(2-hydroxypropyl)aminobenzonitrile (*R*-5). Alternatively, compound 4 is reacted with (*S*)-1-amino-2-propanol according to the foregoing method to yield (*S*)-4-benzyloxy-2-(2-hydroxypropyl)aminobenzonitrile (*S*-5).

Step 2. Compound 5 is reacted with a hydrogen source and a catalyst in a solvent mixture containing water, an acidic component and an organic solvent, to yield (±)-4-benzyloxy-2-(2-hydroxypropyl)aminobenzaldehyde (6). The organic solvent can be

formic acid, which also serves as the acidic component and hydrogen source, or acetic acid, which also serves as the acidic component. Optionally an organic co-solvent can be used, for example pyridine. The hydrogen source can be, for example, hydrogen gas, hypophosphorous acid, or an inorganic hypophosphite salt such as sodium hypophosphite. Preferably the solvent is a mixture of pyridine, acetic acid, and water in a ratio of about 2:1:1 parts by volume. Preferably, the hydrogen source is sodium hypophosphite and preferably the catalyst is Raney nickel. The temperature is 20 to 60 °C, preferably 40 to 45 °C.

[This method is generally described in Fieser and Fieser, Reagents for Organic Synthesis, Volume 1, page 726 (1967).]

Alternatively, compound ***R*-5** is reacted according to the foregoing method to yield (*R*)-4-benzyloxy-2-(2-hydroxypropyl)aminobenzaldehyde (***R*-6**). Alternatively, compound *S*-5 is reacted according to the foregoing method to yield (*S*)-4-benzyloxy-2-(2-hydroxypropyl)aminobenzaldehyde (*S*-6).

Compound **6** is reacted with an organic nitrite, e.g., isoamyl nitrite, in an organic solvent (e.g., tetrahydrofuran), or with an inorganic nitrite, e.g., sodium nitrite, in an organic solvent (e.g., acetic acid), or organic-aqueous solvent pair (e.g., acetic acid-water; tetrahydrofuran -dilute aqueous HCl) to yield (±)-4-benzyloxy-2-(2-hydroxypropyl)nitrosaminobenzaldehyde (7). Preferably the nitrite is sodium nitrite and the solvent is acetic acid-water. Preferably the temperature is kept between about 0 °C and 35 °C. Preferably an inert atmosphere, e.g., nitrogen or argon, is maintained.. The preferred method is to react **6** with about 1.2 molar equivalents of $NaNO_2$ in acetic acid-water (about 4:1 parts by volume) at 15 to 25 °C. The resulting compound 7 can be isolated, but it is preferable instead to convert 7 without isolation to 8 e.g., by a one-flask method as described herein.

Alternatively, compound *R*-6 is reacted according to the foregoing method to yield (*R*)-4-benzyloxy-2-(2-hydroxypropyl)nitrosaminobenzaldehyde (*R*-7). Alternatively, compound *S*-6 is reacted according to the foregoing method to yield (*S*)-4-benzyloxy-2-(2-hydroxypropyl)nitrosaminobenzaldehyde (*S*-7).

Compound 7 is reacted with a reducing agent in an organic solvent optionally containing water to yield (±)-6-benzyloxy-1-(2-hydroxypropyl)indazole (8). Preferably the reducing agent is zinc and the solvent is a mixture of acetic acid and water in a ratio of about 4:1 parts by volume. Most preferably, the reduction is carried out by adding zinc to the reaction mixture in which compound 7 was prepared from compound 6, without isolation of compound 7.

The desired reduction-cyclization reaction of 7 to 8 can be accompanied by a competing denitrosation reaction to regenerate 6. When zinc dust is used as the reducing agent, the ratio of 8 to 6 is about 5:1. The nitrosation-reduction sequence can be repeated on the crude reaction mixture to effect nearly complete conversion of 6 to 8. Alternatively, removal of 6 from the crude product can be effected by chromatography. Alternatively, 6 is removed as a water-soluble hydrazone derivative which is formed by treating the crude product with, e.g., Girard's Reagent T or Girard's Reagent P. Alternatively, 6 is removed as a polymer-bound hydrazone derivative by treating the crude product with a polymer-bound arenesulfonylhydrazide resin.

Alternatively, compound *R*-7 is reacted according to the foregoing method to yield (*R*)-6-benzyloxy-1-(2-hydroxypropyl)indazole (*R*-8). Alternatively, compound *S*-7 is reacted according to the foregoing method to yield (*S*)-6-benzyloxy-1-(2-hydroxypropyl)indazole (*S*-8).

Compound 8 is reacted with an alkanesulfonyl halide or anhydride, or with an arenesulfonyl halide or anhydride, in an organic solvent in the presence of a base, to form

the corresponding sulfonic ester. Preferably an alkanesulfonyl halide is used, most preferably methanesulfonyl chloride. The organic solvent can be pyridine which also serves as the base. Preferably the solvent is dichloromethane and the base is triethylamine. Preferably an inert atmosphere, e.g., nitrogen or argon, is maintained. The sulfonic ester thus obtained is reacted with an alkali metal azide in an organic solvent, to yield (±)-1-(2-azidopropyl)-6-benzyloxyindazole (**9**). Preferably the alkali metal azide is sodium azide and the solvent is preferably a dipolar aprotic solvent, most preferably N,N-dimethylformamide. The temperature can be 25 to 80 °C, preferably about 60 °C, and other temperatures are possible.

Alternatively, compound ***R*-8** is reacted according to the foregoing method to yield (*S*)-1-(2-azidopropyl)-6-benzyloxyindazole (***S*-9**). Alternatively, compound ***S*-8** is reacted according to the foregoing method to yield (*R*)-1-(2-azidopropyl)-6-benzyloxyindazole (***R*-9**).

Compound **9** is reacted with a hydrogen source and a catalyst in an organic solvent, to yield (±)-1-(2-aminopropyl)-6-hydroxy indazole (**10**). Preferably the hydrogen source is ammonium formate, the catalyst is palladium on charcoal and the solvent is ethanol.

Alternatively, compound ***S*-9** is reacted according to the foregoing method to yield (*S*)-1-(2-aminopropyl)-6-hydroxy indazole (***S*-10**). Alternatively, compound ***R*-9** is reacted according to the foregoing method to yield (*R*)-1-(2-aminopropyl)-6-hydroxy indazole (***R*-10**).

The following examples are given to illustrate the preparation of compounds that are the subject of this invention but should not be construed as implying any limitations to the claims.

EXAMPLES

Preparation of (±)-6-benzyloxy-1-(2-hydroxypropyl)indole (2). To a stirred, cooled (10 °C) suspension of NaH (80.7 g of a 60% dispersion in mineral oil, 2.02 mol) in anhydrous THF (1.9 L) was added a solution of 6-benzyloxyindole (**1**) (375 g, 1.68 mol) in anhydrous THF (1.9 L) keeping the temperature below 25 °C. After 2 h at 10 °C, (±)-propylene oxide (140 mL, 2.0 mol) was added dropwise keeping the temperature below 25 °C. After 48 h at 10 °C, (±)-propylene oxide (71 mL, 1.0 mol) was added. After 96 h at 10 °C , saturated aqueous KH_2PO_4 (3.8 L) and ethyl acetate (3.8 L) were carefully added, the layers were separated and the aqueous solution was extracted with 3.8 L of ethyl acetate. The combined organic extracts were dried over sodium sulfate and concentrated in vacuo to yield **2** (520 g, 110%, contains mineral oil).

Preparation of (±)-4-Benzyloxy-2-(N-(2-hydroxypropyl)formamido)benzaldehyde (3). A solution of 172 g of **2** in 1.5 L of dichloromethane was cooled to 78 °C and ozonized (4% ozone in oxygen). Excess ozone was displaced with oxygen for 5 min, followed by addition of 78 mL of dimethyl sulfide and warming to 25 °C. The solution was concentrated to half volume, eluted through Florisil rinsing with ethyl ether-ethyl acetate and concentrated in vacuo. One additional run on 172 g scale and three runs on 58-g scale were performed. The combined products were eluted through silica (2.5 kg) with a gradient of 10%-80% ethyl acetate-hexane to yield, after concentration in vacuo, **3** (351 g, 70%) as an oil.

Preparation of (±)-4-Benzyloxy-2-(2-hydroxypropyl)aminobenzaldehyde (6). An ice-cooled solution of **3** (298 g, 0.95 mol) in THF (3 L) was treated with 1M aq NaOH (1.95 L, 1.9 mol) keeping the temperature below 8° C. After **3** was consumed, the mixture was diluted with brine and extracted twice with ethyl ether. The organic solution was washed with water until neutral and with brine, dried over sodium sulfate, treated

with charcoal and eluted through silica (1 kg) with ether and with 1:1 ethyl acetate-hexane to yield, after concentration in vacuo, **6** (207 g, 76%) as a yellow solid.

Preparation of 4-Benzyloxy-2-fluorobenzonitrile (4). Benzyl bromide (467 mL, 3.93 mol) and potassium carbonate (1.4 kg, 10.1 mol) were added to a solution of 2-fluoro-4-hydroxybenzonitrile (490 g, 3.57 mol) in 3.4 L of acetone. The stirred mixture was heated at 60 °C for 20 h, then cooled and filtered. The filtrate was concentrated and the resulting solid was triturated with 10% ethyl acetate-hexane (5 L) and vacuum dried at 35 °C to yield 4 (787 g, 97%).

Preparation of *(R)*-4-Benzyloxy-2-(2-hydroxypropyl)aminobenzonitrile (*R*-5). A solution of (R)-(-)-1-amino-2-propanol (389 g, 5.19 mol) in DMSO (600 mL) was added to a solution of **4** (786 g, 3.46 mol), basic alumina (786 g), and 4A molecular sieves (131 g). The stirred mixture was heated at 110-140 °C for 24 h, cooled and filtered through Celite, washing with 10 L of 4:1 ether-ethyl acetate followed by 4 L of 3:2 ethyl acetate-hexane. The organic washes were extracted with water (5 L) and the aqueous phase was extracted with four 2-L portions of 25% ethyl acetate-hexane. The combined organic phases were washed with water and brine, dried over sodium sulfate, concentrated to about 4 L and allowed to stand for 48 h. The precipitated solid was collected by filtration, washed with hexane and vacuum dried to provide *R*-5 (first crop 613 g, second crop, 86 g). The concentated supernatant was applied to a 5 kg silica gel pad and eluted with a gradient of 10-50% ethyl acetate-hexane to give, after concentration in vacuo, 119 g of 5, for a total yield of 791 g (81%) of *R*-5.

Preparation of *(R)*-4-Benzyloxy-2-(2-hydroxypropyl)aminobenzaldehyde (*R*-6). Sodium hypophosphite hydrate (986 g, 11.2 mol) and Raney nickel (500 g of a 50% aqueous suspension) were added to a solution of *R*-5 (790 g, 2.8 mol) in 7 L of 2:1:1 pyridine-acetic acid-water. The mixture was stirred at 45 °C for 7 h, then cooled to 25

°C overnight and filtered through Celite rinsing with water and ethyl acetate. The filtrate was washed with saturated Na_2HPO_4 to pH 5, with water and brine, dried over sodium sulfate and concentrated. During concentration, 4 L of heptane was added to azeotropically remove pyridine. After 8 L of solvent had been removed the product solidified. Heptane (5 L) was added and the solid was triturated, isolated by filtration and vacuum dried at 35 °C to yield ***R*-6** (722 g, 90%).

Preparation of *(R)*-6-benzyloxy-1-(2-hydroxypropyl)indazole (*R*-8). Sodium nitrite (209 g, 3.03 mol) was added over 25 min to a stirred solution of ***R*-6** (720 g, 0.2.53 mol) in acetic acid (5.6 L) and water (1.4 L), keeping the temperature below 25° C. The resulting solution of nitrosamine ***R*-7** was cooled in ice, and zinc dust (595 g, 9.10 mol) was added in 25-g portions over 3.5 h, keeping the temperature below 35°C. Ethyl acetate (7 L) was added and the thick suspension was filtered on a sintered glass funnel, washing with ethyl acetate (7.5 L). To the filtrate containing a 5:1 mixture of ***R*-8** and regenerated ***R*-6** was added Girard's Reagent T (98 g, 0.58 mol). After stirring at 25° C for 1 day, another 150 g (0.90 mol) of Girard's Reagent T was added. After 3 more days ***R*-6** was consumed. The mixture was extracted twice with water, with aqueous Na_2HPO_4 to remove acetic acid, with water and brine, dried over sodium sulfate, filtered through Florisil and concentrated. The residue was eluted through 5 kg of silica with 1:1 ethyl acetate-hexane. Clean fractions were concentrated and 4 L of heptane was added to precipitate ***R*-8**. The solid was collected by filtration, washed with 1:1 ethyl acetate-hexane and vacuum dried at 35°C to yield (417 g, 58%) of a yellow solid, composed of 96.7% ***R*-8**, 0.3% ***S*-8** and 3% ***R*-6** by HPLC. Concentration of the supernatant afforded an additional 141 g (20%) of ***R*-8**.

Preparation of (±)-6-benzyloxy-1-(2-hydroxypropyl)indazole (8). The procedure described for ***R*-8** was followed, beginning with (±)-6 (202.7 g, 0.71 mol). After

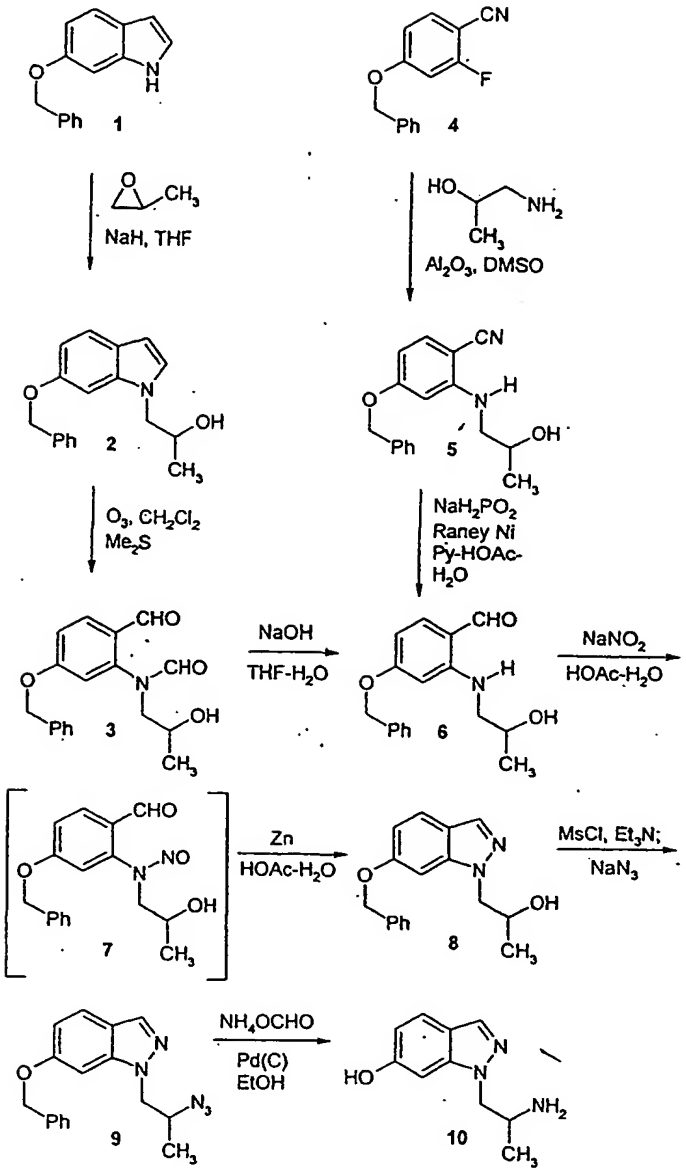
nitrosamine 7 had been converted to a mixture of **8** and **6** (5:1), sodium nitrite (29.5 g, 0.43 mol) was added to renitrosate **6**. Zinc dust (84 g, 1.28 mol) was then added in portions with cooling as described above. When the formation of **8** was complete, the reaction mixture was worked up as described above and combined with the product from another run that started with 176 g of **6**. The combined crude product was purified by chromatography on a Biotage Kiloprep-250 instrument, eluting with ethyl acetate-hexane, to yield **8** (226 g, 60%) of 99% HPLC purity.

Preparation of *(S)*-1-(2-Azidopropyl)-6-benzyloxyindazole (*S*-9). A solution of ***R*-8** (415 g, 1.47 mol) in dichloromethane (4 L) was treated with triethylamine (224 mL, 1.6 mol) and cooled to 0 °C. Methanesulfonyl chloride (125 mL, 1.6 mol) was added keeping the temperature below 25 °C. The mixture was stirred at 25 °C until complete and was then quenched with water (4 L) and stirred vigorously. The layers were separated and the aqueous layer was extracted with an additional 4 L of dichloromethane. The combined organic solutions were dried over sodium sulfate and concentrated in vacuo. The residue was dissolved in DMF (4 L), sodium azide (191 g, 2.94 mol) was added and the mixture was stirred and heated to 70 °C for 16 h, then allowed to cool to 25 °C. Water (16 L) and diethyl ether (5.5 L) were added, the mixture was stirred vigorously and the layers were allowed to separate. The aqueous layer was extracted with diethyl ether (2x7 L), and the combined organic solutions were concentrated and the residue was eluted through silica (6 kg) with 1:3 ethyl acetate/hexane. Product containing fractions were concentrated in vacuo to yield ***S*-9** (380 g, 84%) as an oil.

Preparation of *(S)*-1-(2-Aminopropyl)-6-hydroxyindazole (*S*-10). Ammonium formate (312 g, 4.96 mol) and 10% Pd(C) (38 g) were added to a stirred solution of ***S*-9** (380 g, 1.24 mol) in 4 L of EtOH. After 2 h, another 38 g of 10% Pd(C) was added. The mixture was stirred for 2 h, then filtered through Celite, rinsing with EtOH, and the

filtrate was concentrated. The residue was partitioned between saturated $NaHCO_3$ (4 L) and 1:1 ethyl acetate-THF (5 L). The aqueous phase was treated with 200 g of NaCl and extracted with 2:1 ethyl acetate-THF (3 x 4 L). The combined organic extracts were dried over sodium sulfate, filtered and concentrated in vacuo. The solid residue was suspended in ethyl acetate (3 L), stirred for 0.5 h and filtered to give 200 g of a solid. This material was suspended in THF (1 L) and the mixture was stirred for several minutes and filtered to give a solid, which was washed with cold THF (200 mL), air dried, and then dried for 16 h in vacuo at 45 °C to yield *S*-**10** (183 g, 77%).

SCHEME 1



Other embodiments of the present invention will be apparent to those skilled in the art from consideration of the present specification and practice of the present invention disclosed herein. It is intended that the present specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims and equivalents thereof.

WHAT IS CLAIMED IS:

1. A method of making 1-(2-aminopropyl)-6-hydroxyindazole comprising:

a) nitrosating 4-benzyloxy-2-(2-hydroxypropyl)aminobenzaldehyde to produce 4-benzyloxy-2-(2-hydroxypropyl)nitrosaminobenzaldehyde;

b) reacting said 4-benzyloxy-2-(2-hydroxypropyl)nitrosaminobenzaldehyde with at least one reducing agent to convert NO to NH_2 with concomitant cyclization to form 6-benzyloxy-1-(2-hydroxypropyl)indazole;

c) reacting said 6-benzyloxy-1-(2-hydroxypropyl)indazole with a sulfonyl halide or sulfonic anhydride to form the corresponding sulfonic ester which is reacted with a metal azide to yield 1-(2-azidopropyl)-6-benzyloxyindazole; and

d) reacting said 1-(2-azidopropyl)-6-benzyloxyindazole with at least one hydrogen source and at least one catalyst to yield 1-(2-aminopropyl)-6-hydroxyindazole.

2. The method of claim 1, wherein said nitrosating comprises reacting said 4-benzyloxy-2-(2-hydroxypropyl)aminobenzaldehyde with at least one organic nitrite or at least one inorganic nitrite with at least one organic solvent or organic-aqueous solvent.

3. The method of claim 1, wherein said reducing agent comprises zinc.

4. The method of claim 1, wherein said sulfonyl halide comprises an alkanesulfonyl halide.

5. The method of claim 4, wherein said alkanesulfonyl halide is methanesulfonyl chloride, in the presence of dichloromethane and triethylamine.

6. The method of claim 1, wherein said hydrogen source comprises ammonium formate and said catalyst comprises palladium on charcoal.

7. The method of claim 1, wherein said 4-benzyloxy-2-(2-hydroxypropyl)aminobenzaldehyde is (*R*)-4-benzyloxy-2-(2-hydroxypropyl)aminobenzaldehyde.

8. The method of claim 1, wherein said 4-benzyloxy-2-(2-hydroxypropyl)aminobenzaldehyde is (*S*)-4-benzyloxy-2-(2-hydroxypropyl)aminobenzaldehyde.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/16848

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :C07D 231/56

US CL :548/362.5

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 548/362.5

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Database CAS ONLINE on STN, Chem. Abstr., Accession No. 1998:490629, Vol. 129, No. 136164, MAENO K. et al., 'Preparation of aminoalkylindazole derivatives as 5-HT2c receptor agonists' , WO 9830548, 1998/07/16, abstract.	1-8

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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Date of the actual completion of the international search

09 JULY 2002

Date of mailing of the international search report

24 JUL 2002

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Form PCT/ISA/210 (second sheet) (July 1998)★